TARGETED POLYMERIZED LIPOSOME DIAGNOSTIC AND TREATMENT AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 08/629,056 filed Apr. 8, 1996, now U.S. Pat. No. 6,132,764, which is a continuation-in-part of U.S. Ser. No. 08/286,555 filed Aug. 5, 1994, now U.S. Pat. No. 5,512,294.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to polymerized liposomes which are linked to a targeting agent and may also be linked to at least one of an image contrast enhancement agent and a therapeutic or treatment agent to provide targeted polymerized liposome diagnostic agents and targeted polymerized liposome therapeutic agents, respectively. In one embodiment, this invention relates to liposomes which may be linked to contrast ions for magnetic resonance imaging and radioisotope imaging or optical imaging by using chromophores attached to the liposome or chromophores inherent in the particle in which the polymerization adds stability in vivo. The paramagnetic or radioactive polymerized liposomes may also be linked to antibodies and ligands for specific interaction with biological targets holding the contrast agent to specific biological sites, providing in vitro and in vivo study of the expression of molecules in or on the surface of cells and tissues during disease and pathology. In another embodiment, targeted polymerized liposomes may be linked to or encapsulate a therapeutic agent, such as, for example, proteins, hormones and drugs, for directed delivery of a treatment agent to specific biological locations for localized treatment.

2. Description of Related Art

Liposomes have been used as carriers for administration of drugs and paramagnetic contrast agents. U.S. Pat. Nos. 5,077,057 and 5,277,914 teach preparation of liposome or lipidic particle suspensions having particles of a defined size, particularly lipids soluble in an aprotic solvent, for delivery of drugs having poor aqueous solubility. U.S. Pat. No. 4,544,545 teaches phospholipid liposomes having an outer layer including a modified cholesterol derivative to render the liposome more specific for a preselected organ. U.S. Pat. No. 5,213,804 teaches liposome compositions containing an entrapped agent, such as a drug, which are composed of vesicle-forming lipids and 1 to 20 mole percent of a vesicle-forming lipid derivitized with hydrophilic biocompatible polymer and sized to control its biodistribution and recirculatory half life. U.S. Pat. No. 5,246,707 teaches phospholipid coated microcrystalline particles of bio-active material to control the rate of release of entrapped water soluble biomolecules, such as proteins and polypeptides. U.S. Pat. No. 5,158,760 teaches liposome encapsulated radio-active labeled proteins, such as hemoglobin.

The use of magnetic resonance imaging contrast enhancement agents or radioactive isotopes in the body is practiced by a variety of methods. U.S. Pat. No. 5,135,737 teaches magnetic resonance imaging enhancement agents of paramagnetic metal ion chelates attached to polymers such as polyamine based molecules with antibodies attached for concentration at desired sites in the body. U.S. Pat. Nos. 4,938,947 and 5,017,359 teach an aerosol composition containing soluble fragments of bacterial wall or cell peptidoglycan which may be labeled with a paramagnetic element and encapsulated in liposomes which may be administered as an aerosol. U.S. Pat. No. 5,078,986 teaches magnetic resonance imaging agents of a chelate of a paramagnetic element carried by or within the external surface of a liposome and released at a desired organ or tissue site. PCT Publication Number WO 92/21017 teaches specific liposomes complexed with paramagnetic ions to prolong their blood pool half life and control magnetic resonance relaxivity. Liposomes as MR contrast agents has been reviewed by Unger, E. C., Shen, D. K., and Fritz, T. A., Status of Liposomes as MR Contrast Agents, JMRI, 3, 195–198, (1993).

The need for recirculation of paramagnetic contrast agents in the body, that is avoidance of rapid endocytosis by the. reticuloendothelial system and avoidance of rapid filtration by the kidney, to provide sufficient concentration at a targeted site to afford necessary contrast has been recognized. The use of small molecules, such as gadolinium diethylenetriaminepentaacetic acid, is restricted due to rapid renal excretion while most liposomes, having diameters >800 nm, are quickly cleared by the reticuloendothelial system. Attempts to solve these problems have involved use of macromolecular materials, such as gadolinium diethylenetriaminepentaacetic acid derived polysaccharides, polypeptides, and proteins. These agents have not achieved the versatility in chemical modification to provide for both long recirculation times and active targeting.

Prior attempts to construct bifunctional, ligand-bearing magnetic resonance contrast agents have not been satisfactory due to insufficient sensitivity, poor target specificity and lack of characterization. Gore, J. C. and Smith, F. W., Special Issue: Contrast Agents, Magn. Reson. Img., 3, 1–97, (1985); Hasso, A. N. and Stark, D. D., Special Issue: Contrast Agents, JMRI, 3, 137–310, (1993); and Wehrli, F. W., SMRM Workshop: Contrast Enhanced Magnetic Resonance, Magn. Reson. Med., 22, 177–378, (1991).

Receptor-directed contrast agents for MRI have been attempted using iron oxide particles, but the chemistry and characterization of the particle has been poorly defined and thus it has been difficult to achieve control over non-specific adhesion, blood pool half life and the versatility for both T1 and T2* imaging modes. In addition, no radioisotope imaging is possible using these iron-based agents which further limits their usefulness. Reimer, P., Weissleder, R., Brady, T. J., Baldwin, B. H., Tennant, B. C., and Wittenberg, J., Experimental Hepatocellular Carcinoma: MR Receptor Imaging, Radiology, 180, 641–645 (1991), Reimer, P., Weisslender, R., Lee, A. S., and Brady, T. J., Receptor Imaging: Application to MR Imaging of Liver Cancer, Radiology, 177, 729–734 (1990), Reimer, P., Weissleder, R., Wittenberg, J., and Brady, T. J., Receptor-Directed Contrast Agents for MR Imaging: Preclinical Evaluation With Affinity Assays, Radiology, 182, 565–569 (1992), and Weissleder, R., Reimer, P., Lee, A. S., Wittenberg, J. and Brady, T. J., MR Receptor Imaging: Ultrasmall Iron Oxide Particles Targeted to Asialoglycoprotein Receptors, AJR, 155, 1161–67, (1990).

Antibody MR imaging has been described by Unger, E. C., Totty, W. G., Neufeld, D. M., Otsuka, F. L., Murphy, W. A., Welch, M. S., Connett, J. M., and Philpott, G. W., Magnetic Resonance Imaging Using Gadolinium labeled Monoclonal Antibody, Invest. Radiol., 20, 693–700. (1985), and Weissleder, R., Lee, A. S., Fischman, A. J., Reimer, P., Shen, T., Wilkinson, R., Callahan, R. J., and Brady, T. J., Polyclonal Human Immunoglobulin G Labeled with polymeric Iron Oxide: Antibody MR Imaging, Radiology, 181, 245–249, (1991). In the former case, one is limited by the amount of contrast enhancement that can be achieved by